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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/892,505	06/28/2001	Saluh Kivlighn	50193-109	4997

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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 04/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/892,505	KIVLIGHN ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,7,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *1,5,7,14 and 15* is/are rejected.

7)☒ Claim(s) *NONE* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 5, 7, 14-15 are pending. The Amendment filed on 11/22/2004, amended claims 1, 5, 7 and added new claim 15.

The Applicant's amendment filed on November 22, 2004 is sufficient to overcome the rejection of Claims 1, 5, 7 and 14 under 35 U.S.C. 102(b) as being anticipated by Mentrup et al. (US 4,539,323) of record in the prior Office Action dated 06/22/2004.

The Applicant's amendment filed on November 22, 2004 is sufficient to overcome the rejection of Claims 1, 5, 7 and 14 under 35 U.S.C. 103(a) as being unpatentable over Mentrup et al. (US 4,539,323) of record in the previous Offcie Action dated 06/22/2004.

Claims 1, 5, 7, and 14-15 are examined herein.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/22/2004 has been entered.

Applicant's amendments necessitated the following new rejections.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment with respect to new claim 15 has been fully considered but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for the negative limitation, "uric acid lowering agent is **not losartan**". The original specification merely discloses the method of treating hypertension comprising administration a therapeutically effective amount of an agent capable of reducing uric acid . See page 11, lines 20-23; page 12 lines 20-23, wherein losartan is taught as a uric acid lowering agent.

Any negative limitation or exclusionary proviso must have basis in the original disclosure. See Ex parte Grasselli, 231 USPQ 393 (Bd.App.1983), aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement.

See MPEP § 2163- § 2163.07(b) for a discussion of the written description requirement of 35 U.S.C. 112, first paragraph.

Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 7, 14, 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating hypertension, **does not reasonably provide enablement for a method of preventing hypertension**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention **commensurate in scope** with these claims.

The claims are directed to a method and a composition for treating or **preventing** hypertension. The specification fails to adequately teach how to use the herein claimed method and composition **for preventing hypertension**.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue

experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention:

The rejected claims are drawn to a method and a composition consisting essentially of xanthine oxidase inhibitor for treating or **preventing hypertension**.

(2) Breadth of the Claims:

The instant claims embrace a composition containing a variety of xanthine oxidase inhibitors for treating or **preventing** hypertension.

(3) Guidance of the Specification / Working Examples:

In the instant case, **no** working examples are presented in the specification as filed showing how to **prevent** hypertension in a patient in need of such treatment totally, absolutely, or permanently, not even occurring at the first time.

(4) State/predictabilitv of the Art:

The relative skill of those in the art is high.

However the predictability is low. "To prevent" actually means to anticipate or counter in advance, to keep from happening etc. (as per

Webster's II Dictionary). It is well-known in the state of the art that the cause of hypertension is multifactorial, that is, there are several factors whose combined effects produce hypertension. Hypertension may result from age related changes, environmental toxins, side effects by administration of drugs, genetic factors, high uric acid levels (hyperuricemia) etc. These conditions are caused by various etiologies. For example, hypertension may be due to hyperuricemia, which can be caused by side effects due to administration of cyclosporine. Thus by treating one condition such as hyperuricemia, one cannot prevent hypertension from occurring. The current known treatment of hypertension depends on the patient populations and the severity of the disorders. Some of the disorders, such as primary hypertension, have no known etiology (See Merck manual, page 413). Thus the skilled artisan would view that the **prevention** of hypertension in a patient in need of such treatment totally, absolutely or permanently is highly unpredictable using the composition containing xanthine oxidase inhibitor.

(5) The Quantity of Experimentation Necessary:

There is no working example provided for the prevention of hypertension. Therefore, Applicant fails to provide information sufficient to practice the claimed invention, absent **undue experimentation**.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its

successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors, e.g., the amount of direction or guidance provided, absence of working examples, and the predictability of the art discussed above, to practice the claimed invention herein, a person of skill in the art would have to test a variety of xanthine oxidase inhibitors in the instant claims to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Accordingly the claims are evaluated as method of treating hypertension and not method of **preventing** hypertension.

Claims 1, 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for xanthine oxidase inhibitor such as allopurinol and carprofen for the treatment of hypertension, **does not reasonably provide enablement for any substance or compounds represented by xanthine oxidase inhibitor in general**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention **commensurate in scope** with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation**.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of treating hypertension by administering xanthine oxidase inhibitor. The nature of the invention is complex in that it encompasses the treatment of hypertension comprising administering **any** xanthine oxidase inhibitor.

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass treatment of hypertension by administering **any xanthine oxidase inhibitor**.

(3). Guidance of the Specification / (4) Working Examples:

The guidance given by the specification as to what type of xanthine oxidase inhibitor would be effective for the treatment of

hypertension is limited. The only examples provided are with a xanthine oxidase inhibitor allopurinol. See page 21, EXAMPLE 2; page 22, EXAMPLE 3.

(5). State of the Art:

While the state of the art is relatively high with regard to specific xanthine oxidase inhibitor for the treatment of hypertension, the state of the art with regard to xanthine oxidase inhibitors in **general** is underdeveloped. Different xanthine oxidase inhibitor have different chemical structures and are expected to behave in different manners, evidence that the level of skill in this art is low relative to the difficulty of the task of determining a suitable xanthine oxidase inhibitor for the treatment of hypertension.

(6). Predictabilitv of the Art:

The invention is directed to xanthine oxidase inhibitor **in general** for the treatment of hypertension. It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970).

It is further noted that the pharmaceutical art is **unpredictable**, requiring each embodiment to be individually assessed for physiological activity. For example it is known in the art that oxypurinol (also known as alloxanthine) a xanthine oxidase inhibitor is a uric acid

lowering agent. The effect of xanthine oxidase inhibitors such as 4-amino-6-hydroxypyrazolo[3,4-d]pyrimidine(AHPP), allopurinol and oxypurinol on blood pressure was studied by Miyamoto et al. (Proceedings of the Society for Experimental Biology and Medicine 1996, 211(4), 366-73) in animal model. It was reported that AHPP reduced the blood pressure of SHR rats to 70 % of the initial pressure; this is almost the blood pressure of normal rats, whereas only 10 % reduction of hypertension was observed with iv injection of oxypurinol(alloxanthine). Thus even the structurally closely related uric acid lowering agent, a xanthine oxidase inhibitor, such as AHPP, and oxypurinol have very different ability of treating hypertension. Thus in the instant case, it is highly **unpredictable** to treat hypertension using **any** xanthine oxidase inhibitor or **any** uric acid lowering agent. Also one skilled in the art would recognize that it is highly unpredictable with regards to not only therapeutic effects, but also side effects, and especially serious toxicity due to drug accumulation or that may be generated by drug-drug interactions when and/or after administering to a host any agents represented by either a xanthine oxidase inhibitor and/or while the patient also administers other medicines. One of skill in the art would not be able to fully predict the possible treatment of hypertension herein and possible adverse effects occurring with many agents having the claimed functional properties. Thus, the instant claimed invention is highly unpredictable.

(7). The Quantitv of Experimentation Necessary:

In order to practice the claimed invention, one of skill in the art would have to first envision a specific xanthine oxidase inhibitor, a pharmaceutical carrier, a dosage for each xanthine oxidase inhibitor, the duration of treatment, route of treatment, etc. One of skill in the art would then need to test specific xanthine oxidase inhibitor in the model system to determine whether or not it is effective for treating hypertension and one would need to test for side effects and toxicity. If the treatment is unsuccessful, one of skill in the art would have to modify the first xanthine oxidase inhibitor, dosage, duration of treatment, route of administration, etc. Even if successful, however, one of skill in the art would then need to determine the magnitude of the side effects and toxicity of utilizing xanthine oxidase inhibitor. One of skill in the art would then need to determine whether or not the magnitude of the side effects could be reduced by increasing or decreasing the dosage of xanthine oxidase inhibitor while retaining the functional aspect. Once the functionality to toxicity ratio was maximized, one of skill in the art would need to determine whether or not the xanthine oxidase inhibitor which had been used was of sufficient benefit that it would serve as useful for treating hypertension. If not, one would need to select another xanthine oxidase inhibitor agent and repeat the process until a sufficient benefit to detriment ratio had been achieved.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for uric acid lowering agent such as allopurinol, carprofen, losartan, benzbromaraone, benziodarone, probenecid, sulfinpyrazone ethebencid, orotic acid, ticrynafen and zoxazolamine, enalapril,, L-arginine **does not reasonably provide enablement for "the** uric acid lowering agent" **in general** for the treatment of hypertension. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention **commensurate in scope** with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation**. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount

of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of treating hypertension by administering uric acid lowering agent. The nature of the invention is complex in that it encompasses the treatment of hypertension comprising administering **any** uric acid lowering agent.

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass treatment of hypertension by administering **any** uric acid lowering agent.

(3). Guidance of the Specification:

The guidance given by the specification as to what type of uric acid lowering agent would be effective for the treatment of hypertension is limited. All of the guidance provided by the specification regarding uric acid lowering agents is directed to the following agents: xanthine oxidase inhibitor, such as allopurinol, and carprofen; uricosuric agents such as losartan, benzbromaraone, benziodarone, probenecid, sulfinpyrazone ethebencid, orotic acid, ticrynafen and zoxazolamine; ACE inhibitor, enalapril, and L-arginine a substrate for nitric oxide production. Beyond these agents, there is no

guidance in the specification regarding what type of other agents, compounds or otherwise, would be effective as an uric acid lowering agent for the treatment of hypertension.

(4) Working Examples:

Applicant merely shows the treatment of hypertension with the three specific uric acid lowering agents, allopurinol, losartan, and L-Arginine. See EXAMPLES 2, 3, 4 on pages 221-23 of the specification.

(5). State of the Art:

While the state of the art is relatively high with regard to specific uric acid lowering agent for the treatment of hypertension, the state of the art with regard to uric acid lowering agent in **general** is underdeveloped. Different uric acid lowering agent are expected to have different chemical structures and behave in different manners, evidence that the level of skill in this art is low relative to the difficulty of the task of determining a suitable uric acid lowering agent.

(6). Predictability of the Art / (7). The Quantity of Experimentation Necessary:

As discussed above for xanthine oxidase inhibitor.

Further, these recitations "xanthine oxidase inhibitor" and "uric acid lowering agent" may broadly encompass those known and **unknown** compounds having the recited functions as of the instant filing date, as discussed above. Note those **future known** compounds yet to be discovered and/or made. Hence,

those unknown or future known compounds encompassed by claim 1, 5, 7, 14, 15 herein must require to additional or future research to discover, establish or verify their usefulness. Therefore, as indicated above the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 (b) that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Baldwin (US 4,058,614).

The instant invention is drawn to a method of treating hypertension comprising administering a composition comprising essentially of an xanthine oxidase inhibitor and a composition comprising a xanthine oxidase inhibitor.

Baldwin discloses specific novel imidazole compounds which are active as xanthine oxidase inhibitors useful in a method of treatment of hypertension. A pharmaceutical composition for inhibiting xanthine oxidase comprising these novel substituted imidazole compounds is also disclosed. See column 1, lines 7-33; column 9, claim 14.

Claims 1, 5, 7, 14, 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyamoto et al. (Proceedings of the Society for Experimental Biology and Medicine 1996, 211(4), 366-73).

Miyamoto et al. discloses the inhibition of xanthine oxidase by three types of pyrazolopyrimidine derivatives. Kinetic studies indicated that allopurinol inhibited the conversion of xanthine to uric acid catalyzed by xanthine oxidase. See page 368, left bottom paragraph. A composition containing allopurinol in 1 ml of 0.1 N NaOH is also taught. See page 368, lines 16-20. Miyamoto further teach a method of treating hypertension in spontaneously hypertensive rats. Treatment with allopurinol at a dose of 45.4 mg/kg showed decrease in blood pressure. See page 370, right hand column, lines 8-11.

It is respectfully pointed out that for the purposes of searching for and applying prior art under 35 USC 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to comprising. If an applicant contends that additional steps or material in the prior art are excluded by the recitation of "consisting essentially of ", applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. See MPEP 2111.03.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on 8 am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

4/4/05

SHAOJIA A. JIANG, PH.D.
PRIMARY EXAMINER